REMARKS

I. Amendments to the Claims

Claims 23 and 73 have been amended to clearly define the subject matter. The claims are supported by the originally filed specification, for example, page 5, lines 20-27, and page 9, lines 17-19. No new matter has been added.

Claims 23, 29, 73, and 76-77 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. Arguments and Response to Rejection

1. The Written Description Rejection Should Be Withdrawn

Claims 23, 29, 73 and 76-77 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action at pages 2-4. The Office Action correctly recognizes that the claims are drawn to methods of treating a blood-born tumor or leukemia, and not graft-versus-host disease (GVHD). *Id.* However, the Office Action contends that "there is no basis in the originally filed disclosure for the exclusion of GVHD patients from the claimed methods." *Id.* Applicant respectfully disagrees with the rejection.

The test for sufficiency of written description is whether the disclosure of the application "reasonably conveys to the artisan that the inventor had possession" of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); accord *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; see also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement. *See, e.g., In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996) (stating that "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, *even if [not] every nuance of the claims is explicitly described in the specification*, the adequate written description requirement is met") (emphasis added).

Applicant respectfully submits that the instant specification provides ample teaching of the claimed subject matter. For example, the specification at page 5, lines 20-27 states as follows:

"It should be noted that angiogenesis has been associated with blood-born tumors such as leukemias, any of various acute or chronic neoplastic diseases of the bone marrow in which unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia-like tumors."

Also, the specification at page 9, lines 17-19 states as follows:

"It is yet another object of the present invention to provide a method and composition for the treatment of blood-born tumors such as leukemia."

Accordingly, a person of ordinary skill would view the specification as providing sufficient written description support for treatments of blood-born tumors and leukemia. There is no description in the specification that the methods of treatment relate to treating graft-versus-host disease or that the methods of the invention were for graft-versus-host disease in blood-born tumor patients. Indeed, the treatment of graft-versus-host disease with thalidomide was known in the art by TNF-α inhibition or immunosuppressive properties of thalidomide, neither of which is anti-angiogenesis action.[1] *See e.g.,* U.S. Patent No. 5,385,901 to Kaplan *et al.* (column 2, lines 47-50) and reference cited in IDS in this application (*e.g.,* C247 filed November 7, 2007, Heney, D., *et al.*, "Thalidomide treatment for chronic graft-versus-host disease", *British J. of Haematology*, 1991, vol. 78, pp. 23-27). The claimed invention is directed to the treatment of blood-born tumors, not the treatment of graft-versus-host disease. Applicant invented and wishes to claim the treatment of blood-born tumors via anti-angiogenesis. Thus, Applicant is claiming treatment of patients having blood-born tumors, not graft-versus-host disease. The claims were amended to make this distinction clear. Thus, one skilled in the art would understand that the claimed methods are drawn to the treatment of blood-born tumor patients that do not have graft-versus-host disease. Applicant respectfully submits that Applicant should be entitled to claim an invention in a manner as Applicant seeks for the best possible protection.

In addition, what is *conventional or well known to one of skill in the art* need not be disclosed in detail (*Id.* at p. 1105, column 3, *ll.* 39-41, emphasis added) and, where the *level of knowledge and skill in the art is high*, a written description question should not be raised.

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[1] To the extent that the Examiner believes that there may be a patient that has leukemia and graft-versus-host disease and that such patient may be treated with thalidomide, Applicant submits if the administration is for immunosuppression to treat graft-versus-host disease, it is not encompassed by the claimed invention as the claim language clearly recites treating only blood-born tumors.

See the Guidelines for Examination of Patent Applications Written Description Requirement (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), at p. 1106, column 1, *ll.* 34-36 (emphasis added). Applicant respectfully points out that compliance with the written description requirement does not require the specific disclosure of every permutation of an invention, but should merely be commensurate with knowledge that comprises the state of the art. *See Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005). From the specification and the instant claims, a skilled person would understand that the inventor possessed methods for treating blood-born tumor patients that do not have graft-versus-host disease. In view of *Capon*, the specification's disclosure, and the knowledge in the art at the time of filing, the disclosure provided *is,* in fact, sufficient to demonstrate to one of skill in the art that Applicant were in possession of the subject matter of the pending claims at the time of filing.

The Office Action has not satisfied the burden of proving a *prima facie* case of failing to comply with the written description requirement. According to well-established law, a *prima facie* case requires "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the claimed invention." *Alton*, 76 F.3d at 1175 (quoting *In re Wertheim*, 541 F.2d 257, 263 (C.C.P.A. 1976)). The Office Action has not presented any reasons why persons in the art would not recognize that the present application discloses the invention as claimed. *See Alton*, 76 F.3d at 1175.

In view of the foregoing, the disclosure clearly supports for the methods of treating blood-born tumors and leukemia, as claimed. Applicant was clearly in possession of the invention as of the filing date of this application. Because the Office Action does not meet its burden of proving a *prima facie* case of failing to satisfy the written description requirement, Applicant respectfully submits that the rejection is improper and should be withdrawn.

2. OLSON Does Not Render the Claimed Invention Obvious

The Office alleges the rejection of claims 23, 29 and 76-77 under 35 U.S.C. § 103(a) as being unpatentable over OLSON *et al.* (*Clinical Pharmacology and Therapeutics*, 1965, vol. 6, no. 3, pages 292-297, "OLSON"). (Office Action, pages 4-6). The Office contends that (1) OLSON discloses oral administration of thalidomide to patients with advanced malignancy, two of the treated patients having multiple myeloma; (2) in one patient with multiple myeloma, "the rapid progression of the disease appeared to be slowed"; (3) both multiple myeloma patients showed "subjective improvement" (Table 1); and (4) it is clear that thalidomide was effective to "treat" patients having multiple myeloma by slowing

disease progression and providing subjective improvement to the treated patients. *Id.* Applicant respectfully traverses this rejection.

OLSON Does Not Suggest that Thalidomide is Effective to Treat Tumor

OLSON reports that thalidomide was administered to 21 patients with 14 tumor types for between 1 and 34 weeks. All but two of the patients who took thalidomide died either during or shortly after the trial had finished (OLSON, Table I). In the words of the authors, the study *"does not constitute an adequate drug trial in any form of cancer treated"* (page 296, under "*Discussion*"). The authors of OLSON themselves even conclude that "*In **no** instance was there evidence of objective regression of disease*" (page 293, last full sentence), that "*there was **no** objective evidence of tumor regression*" (page 296, sentence spanning 1st and 2nd column), and that *"Twenty-one patients with fourteen types of tumor were treated with thalidomide for 1 to 34 weeks (total dose 4.2 to 354.0 Gm) **without** objective evidence of tumor regression"* (page 296, Summary).

In particular, OLSON states that in patients 13 (multiple myeloma) and 17 (fibrosarcoma), *"the rapid progression of the disease appeared to be slowed, but measurements did not show regression"* (the passage bridging pages 293 to 295). Table I describes that patient 13 (multiple myeloma) has *"progressive disease"* and "*died after 8 weeks of treatment"* (page 295, Table I). Patient 14 (multiple myeloma) was reported to have *"progressive disease"* and *"lost to follow-up; stopped treatment."* *Id.* Patient 17 showed *"possible arrest of tumor growth; eventually progressive"* and "*died 34 weeks on treatment."* *Id.*

Therefore, neither the results set out in OLSON, nor the authors' own discussion of them, discloses or even hints at using thalidomide in an effective treatment of any type of tumor. Despite the report and conclusions drawn by OLSON, the Office Action alleges that OLSON teaches that thalidomide was effective to treat multiple myeloma patients by slowing disease progression.

In fact, when reading the teaching of OLSON, a skilled artisan would have understood that thalidomide is not effective in treating any tumors, because thalidomide had no objective effects on tumor regression. Accordingly, OLSON teaches away from the claimed methods of treating blood-born tumors, and there is no motivation to treat any tumors. The Office has not pointed to any reason that would have prompted a person skilled in the art to treat blood-born tumors as claimed.

Further to support that OLSON teaches away from the claimed invention and there is no motivation to treat tumors, Applicant respectfully submits herewith Declarations of

Professor Morgan (EXHIBIT 1) and Dr. Ohno (EXHIBIT 2). These Declarations were filed before the European Patent Office in an appeal to a decision issued by the Opposition Division in opposition to the corresponding European Patent No. 1264597. OLSON was cited as a reference in the opposition to the European Patent. In the appeal to the decision by the Opposition Division, Dr. Ohno and Professor Morgan opined on the teachings of OLSON. They confirm what results in OLSON study actually suggest to a skilled artisan about the efficacy of the drug on trial.

In his declaration, Dr. Ohno has expressed the view that *"OLSON does not disclose or provide any evidence of a therapeutic effect of thalidomide against any of these 21 tumors. Rather, from the points of an oncologist, it actually teaches that thalidomide was not effective in any tumor tested"* (EXHIBIT 2, paragraph 7).

Likewise, in his declaration, Professor Morgan is of the clear opinion that OLSON does not disclose thalidomide to have shown any *"efficacy whatsoever for patients with any of the malignancies"* (EXHIBIT 1, paragraph 11). He also concludes that *"None of them* (the patients in the study) *showed objective evidence of any improvement in their malignancy, and the obvious conclusion would have been that it* (thalidomide*) was ineffective as an anti-cancer drug."* (EXHIBIT 1, paragraph 19).

These views are consistent with the views of the authors of OLSON, not those of the Office Action.

Nonetheless, the Office Action alleges that the skilled artisan would have been motivated to use thalidomide in multiple myeloma patients and there would be a reasonable expectation that thalidomide would be effective to "treat" multiple myeloma patients by providing subjective improvement to patients (pages 5-6). Applicant respectfully disagrees.

OLSON merely discloses subjective improvement (*e.g.*, better sedation) in seven patients (Abstract, Tables I and III, and page 295, left hand column). Because thalidomide was a known sedative drug, this subjective improvement would have been expected but it is not tumor treatment. *See* EXHIBIT 1, paragraph 12 and EXHIBIT 2, paragraph 9. As Professor Morgan confirms in his declaration (paragraphs 8 and 13), subjective improvement is a *"totally separate"* concept from treating a tumor, and it does not have *"any implications for a mode of action directly against the tumor itself."* Dr. Ohno also states that OLSON merely refers to subjective improvement but OLSON does not show thalidomide to be an anti-tumor agent (EXHIBIT 2, paragraphs 8 and 9).

A further reason for viewing the results described in OLSON with caution is that *"All patients had been previously treated with one to five antitumor agents"* before the course of

treatment with thalidomide (page 295, left-hand column, lines 6-8). OLSON does not provide any information concerning what these anti-tumor agents were. Accordingly, it is possible that the responses reported in patients 13 and 14 (multiple myeloma), and/or any of the subjective improvements seen in any of the other patients, were caused by one or more anti-tumor agents that were administered to the patients before the thalidomide trial even began, and possibly during the trial itself.

In view of the foregoing, OLSON does not teach or suggest any effectiveness of thalidomide in treating any tumor. OLSON does not include any information from which it could be concluded that thalidomide could be used to treat tumors. In fact, the authors conclude to the contrary and oncologists at the time read as so.

The accuracy of this conclusion, from the point of view of the skilled person, is confirmed by both Professor Morgan and Dr. Ohno:

"I would say that OLSON in fact showed no efficacy whatsoever for patients with any of the malignancies. There is nothing in OLSON that would lead me to conclude that any patient had improved at all. There was no data disclosed whatsoever that would lead a Clinician to suspect that the drug was useful, and to use it in further cancer patients. Nor would anything in OLSON's report lead a Clinician to treat any particular tumor patient with this drug with the aim of obtaining a direct response on tumor size." (EXHIBIT 1, paragraph 11).

"OLSON does not disclose or provide any evidence of a therapeutic effect of thalidomide against any of these 21 tumors. Rather, from the point of an oncologist, it actually teaches that thalidomide was not effective in any tumor tested." (EXHIBIT 2, paragraph 7).

In addition, the published documents provide further evidence to support the views of Professor Morgan and Dr. Ohno that OLSON did not teach or suggest one skilled in the art to use thalidomide in treating tumors. In fact, many publications, which were cited in the Response of April 19, 2007, discuss the negative results in OLSON. *See e.g.,* Diggle, Glasmacher, Kumar and Rajkumar, and pages 11-12, 15 and 16 of the April 19, 2007 Response. The publications confirm that any interest in testing thalidomide in cancer therapy disappeared for about 30 years since 1965 (OLSON publication date) due to the established view that OLSON taught the skilled person absolutely nothing about the efficacy of thalidomide for treating cancer. *See* EXHIBIT 1, paragraph 16, and EXHIBIT 2, paragraphs 13-14.

Further, documents published before the priority date of the application also confirm that OLSON had been completely dismissed as providing any disclosure that thalidomide exhibited any anti-tumor activity. *See e.g.,* Roe, *The Practitioner* (1974) cited as C363 reference in IDS filed on February 25, 2009. Applicant submits a copy of the reference as EXHIBIT 3, in order to establish that OLSON revealed no evidence that thalidomide exhibited useful anti-cancer activity. Roe at page 297 states that:

> *"Furthermore, two clinical trials (Olsen et al, 1965 (i.e. OLSON); Grabstald and Golbey, 1965) involving a total of 92 cancer patients revealed no real evidence that thalidomide exhibited useful anti-cancer activity...". [Emphasis added]*

Thus, at the priority date of the present application, a skilled person would never have considered it obvious to try using thalidomide to treat tumors, with any reasonable expectation of success. Applicant respectfully requests that OLSON cannot render the claimed methods obvious.

Unexpected Results Rebut A *Prima Facie* Case of Obviousness

Applicant respectfully submits that even assuming, *arguendo*, that a *prima facie* case of obviousness were established, the record contains evidence of unexpected results for the instant methods that rebut any such *prima facie* case. The PTO is required to consider all rebuttal evidence submitted by an applicant. *See, e.g.*, MPEP §2145. This requirement remains unchanged following *KSR*, as the Federal Circuit has made clear. *See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *also* 2010 KSR Guidelines Update to obviousness guidelines (published in the September 1, 2010 Federal Register at Volume 75, Number 169, p. 53463-53660), at p. 53657-53658. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *Id.* at 1351.

Indeed, in Response filed on February 3, 2010 (pages 6-7), Applicant explained the unexpected results of the claimed methods in treating blood-born tumors such as leukemia, lymphoma, and multiple myeloma. Applicant submitted many publications showing the unexpected results of the claimed methods[2]. *See* C318-C334 filed on March 14, 2008. These publications were also filed as C317-C333 in a divisional application no. 11/096,155, and

[2] The articles were submitted to the Office on April 19, 2007, July 12, 2007, October 31, 2007, March 14, 2008 and Feb. 25, 2009, together with supplemental IDS and list of references cited (*e.g., see* C318-C334 and C347-373 references). All of these references were made of record in the file history of the application.

were recognized by the PTO in Notice of Allowability of the divisional as evidence of the unexpected results in treating blood-born tumors (page 2 of Notice of Allowability dated January 12, 2010). The divisional application no. 11/096,155 issued U.S. Patent No. 7,723,361.

Applicant respectfully submits that the publications in the record as a whole support the unexpected results of the claimed invention using thalidomide in treating blood-born tumors, and that these results are sufficient to rebut any presumption of obviousness. The PTO must consider evidence submitted to rebut alleged obviousness of the claimed invention. Thus, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.

3. The Obviousness-Type Double Patenting Rejection Should Be Withdrawn

On pages 6-7 of the Office Action, claims 23, 29, 73 and 76-77 are rejected under the judicially-created obviousness-type double patenting over claims 1-4 and 6 of U.S. Patent No. 7,435,745 and over claims 21-30 of Application No. 12/249,847 ("the '847 application"). Applicant respectfully disagrees.

Solely to promote the allowance of the case and without acquiescing to the Examiner's rejections, terminal disclaimers over the cited patent and application are submitted herewith. Thus, this rejection is moot and should be withdrawn.

III. Conclusion

Applicant respectfully requests that the above amendment and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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